GUAIFENESIN SUSTAINED RELEASE FORMULATION AND TABLETS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a sustained release guaifenesin formulation for oral administration and methods of its manufacture. In particular, it relates to a sustained release guaifenesin formulation which maintains a therapeutically effective blood concentration of guaifenesin for a duration of at least twelve hours without an increase in dosage strength. The present invention further relates to a modified release bi-layer guaifenesin tablet which demonstrates a maximum serum concentration equivalent to an immediate release tablet yet maintains a therapeutically effective blood concentration of guaifenesin for a duration of at least twelve hours.

2. Description of Related Art

Sustained release pharmaceutical formulations provide a significant advantage over immediate release formulations to both clinicians and their patients. Sustained release dosage forms are administered to patients in much fewer daily doses than their immediate release counterparts and generally achieve improved therapeutic effect and efficiency in the fewer daily doses.

For example, a 400 mg immediate release dosage form of an active ingredient (hereinafter "drug" or "medicament") with a short half-life, such as guaifenesin, may have to be administered to a patient three times within 12 hours to maintain adequate bioavailability of the drug to achieve therapeutic effect. This results in a series of three serum concentration profiles in the patient in which there is a rapid increase of drug followed by a similar rapid decrease. Such rapid increases and decreases provide a patient with a short window of appropriate blood concentration of the medicament for optimum therapy. A 1200 mg sustained release dosage form, on the other hand, may only have to be administered to a patient once every 12 hours to achieve therapeutic effect. Sustained release dosage forms generally control the rate of active drug absorption, so as to avoid excessive drug absorption while maintaining effective blood concentration of the drug to provide a patient with a consistent therapeutic effect over an extended duration of time.

Besides reducing the frequency of dosing and providing a more consistent therapeutic effect, sustained release dosage forms generally help reduce side effects caused by a drug. Because sustained release dosage forms deliver the drug in slow, incremental amounts versus the cyclic high and low concentrations of immediate release formulations, it is easier for a patient's body to digest the drug, thereby avoiding undesirable side-effects. For patients who self-administer therapies, sustained release dosage forms generally result in greater compliance due to the lower frequency of dosing, lower quantity of dosage units to be consumed, and reduced undesired side-effects.

Sustained release formulations for the sequential or timed release of medicaments are well known in the art. Generally, such formulations contain drug particles mixed with or covered by a polymer material, or blend of materials, which is resistant to degradation or disintegration in the stomach and/or in the intestine for a selected period of time. Release of the drug may occur by leeching, erosion, rupture, diffusion or similar actions depending upon the nature of the polymer material or polymer blend used.

Conventionally, pharmaceutical manufacturers have used hydrophilic hydrocolloid gelling polymers such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, or Pullulan to formulate sustained release tablets or capsules. These polymers first form a gel when exposed to an aqueous environment of low pH thereby slowly diffusing the active medicament which is contained within the polymer matrix. When the gel enters a higher pH environment such as that found in the intestines, however, it dissolves resulting in a less controlled drug release. To provide better sustained release properties in higher pH environments, some pharmaceutical manufacturers use polymers which dissolve only at higher pHs, such as acrylic resins, acrylic latex dispersions, cellulose acetate phthalate, and hydroxypropyl methylcellulose phthalate, either alone or in combination with hydrophilic polymers.

Generally, these formulations are prepared by combining the medicament with a finely divided powder of the hydrophilic polymer, or the hydrophilic and water-insoluble polymers. These ingredients are mixed and granulated with water or an organic solvent and the granulation is dried. The dry granulation is then usually further blended with various pharmaceutical additives and compressed into tablets.

Although these types of formulations have been successfully used to manufacture dosage forms which demonstrate sustained release properties, these formulations generally do not have the desired release profile or serum concentration of medicament over

an extended period of time. These sustained release formulations generally result in a delay in the appearance of drug in the blood stream, thereby delaying therapeutic effect. Additionally, when the drug does appear, its maximum serum concentration (Cmax) is lower than the maximum concentration required for the most effective therapeutic result. Furthermore, most formulations which claim twelve hour potency release almost all of their drug within six to eight hours, making the formulation less therapeutically effective towards the end of the twelve hour period. To prevent blood serum concentrations of active drug from falling below a therapeutically effective level at extended time periods, many manufacturers increase the drug strength of the dosage form. The increase in drug strength, however, results in a concomitant increase in side-effects.

To improve the release profile of certain sustained release dosage forms, some pharmaceutical manufacturers have made tablets and capsules which comprise a combination of an immediate release formulation and a sustained release formulation. Although this solution improves the Cmax and length of time before the drug appears in the blood stream in some formulations, the extended therapeutic effect is not improved.

Furthermore, every medicament has different solubility properties and pH dependencies which affect its dissolution rate, and hence its bioavailability. Bioavailability can also be affected by a number of factors such as the amounts and types of adjuvants used, the granulation process, compression forces (in tablet manufacturing), surface area available for dissolution and environmental factors such as agitation in the stomach and the presence of food. Due to these numerous factors, specific formulations play an important role in the preparation of prolonged action solid dosage forms, particularly in the preparation of solid dosage forms which achieve appropriate bioavailability for optimum therapeutic effect.

Guaifenesin is known chemically as 3-(2-methoxyphenoxy)-1,2-propanediol. It is an expectorant, a drug which increases respiratory tract fluid secretions and helps to loosen phlegm and bronchial secretions. By reducing the viscosity of secretions, guaifenesin increases the efficiency of a cough reflex and of ciliary action in removing accumulated secretions from trachea and bronchi. Guaifenesin is readily absorbed from the intestinal tract and is rapidly metabolized and excreted in urine. Guaifenesin has a typical plasma half-life of approximately one hour. Because of the rapid metabolization and excretion of guaifenesin, typical immediate release dosage tablets of guaifenesin provide only a short window of therapeutic effectiveness for patients resulting in the various recognized problems described above.

None of the prior art has described a sustained release dosage form of guaifenesin which is capable of sustaining therapeutic effective for at least twelve hours. Likewise, none of the prior art has described a sustained release dosage form of guaifenesin which has a Cmax equivalent to that of an immediate release formulation, appears in the blood stream as quickly as an immediate release formulation, yet sustains therapeutic effect for at least twelve hours.

SUMMARY OF THE INVENTION

The present invention overcomes the problems and disadvantage associated with current strategies and designs in formulation of modified release guaifenesin dosage forms.

This invention relates to a novel sustained release pharmaceutical formulation comprising guaifenesin. The sustained release formulation may comprise a combination of at least one hydrophilic polymer and at least one water-insoluble polymer. The total weight ratio of hydrophilic polymer to water-insoluble polymer may be in a range of about one-to-one (1:1) to about six-to-one (6:1), more preferably a range of about three-to-two (3:2) to about four-to-one (4:1), and most preferably about two-to-one (2:1). When a tablet comprising the sustained release formulation is exposed to an aqueous medium of low pH, such as that found in the stomach, the polymer combination gels causing guaifenesin to diffuse from the gel. When the tablet passes to the intestines where an aqueous medium of higher pH is present, the gel begins to dissolve, thereby releasing guaifenesin in controlled amounts. The tablet is capable of releasing therapeutically effective amounts of guaifenesin over an extended period, i.e. twelve or more hours.

This invention also relates to a modified release guaifenesin tablet which comprises two discrete portions (a bi-layer tablet), a rapid release portion and a sustained release portion, each portion comprising a specific quantity of guaifenesin. The rapid release portion is formulated to dissolve in aqueous acidic medium, such as that found in the stomach, to quickly release guaifenesin contained within the portion. The sustained release portion may comprise a combination of hydrophilic polymer in a ratio range of about one-to-one (1:1) to about six-to-one (6:1), more preferably a range of about three-to-two (3:2) to about four-to-one (4:1), and most preferably about two-to-one (2:1, with a water-insoluble polymers as described above.

The present invention also relates to modified release guaifenesin preparations of the type described above in the form of capsules having beads of both rapid release formulation and beads of sustained release formulation.

The bi-layer tablet of the present invention demonstrates a maximum serum concentration (Cmax) and time of availability in the blood stream that are equivalent to an immediate release tablet. The bi-layer tablet also provides sustained release of guaifenesin over at least a twelve hour period from one dose. The bi-layer tablet of the present invention further maintains serum concentration levels of guaifenesin at a therapeutically effective level for at least a twelve hour period without an increase in the drug strength of the dosage form.

The present invention also relates to methods of manufacturing sustained release formulations and bi-layer guaifenesin tablets of the present invention. An example of a manufacturing method for a sustained release formulation comprises mixing a hydrophilic polymer and active ingredients in a mixer, adding water to the mixture and continuing to mix and chop, drying the mixture to obtain hydrophilic polymer encapsulated granules, milling and screening the resulting granulation, and blending it with various pharmaceutical additives, additional hydrophilic polymer, and water insoluble polymer. The formulation may then be tableted and may further be film coated with a protective coating which rapidly dissolves or disperses in gastric juices.

An example of a bi-layer tablet manufacturing method comprises blending a quantity of guaifenesin with various excipients, colorants, and/or other pharmaceutical additives to form a rapid release formulation, blending another quantity of guaifenesin with a hydrophilic polymer, a water-insoluble polymer, and various excipients, colorants, and/or other pharmaceutical additives to form a sustained release formulation, and compressing a quantity of the rapid release formulation with a quantity of the sustained release formulation to form a bi-layer tablet. The tablet may then be optionally coated with a protective coating which rapidly dissolves or disperses in gastric juices.

Other objects, advantages and embodiments of the invention are set forth in part in the description which follows, and in part, will be obvious from this description, or may be learned from the practice of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a flow diagram depicting steps in a wet granulation method for manufacturing the sustained release formulation of the present invention.

Figure 2 is a flow diagram depicting steps in a dry granulation method for manufacturing the sustained release formulation of the present invention.

Figure 3 is a flow diagram depicting steps in a method for manufacturing the bi-layer tablet of the present invention.

Figure 4 is a graph demonstrating the dissolution profiles of tablets comprising two different sustained release formulations of the present invention.

Figure 5 is a graph demonstrating the dissolution profiles of an immediate release dosage form and two sustained release dosage forms of guaifenesin, all of which are known in the art.

Figure 6 is a graph demonstrating the plasma concentration of guaifenesin over time in healthy human volunteers who were dosed three different guaifenesin formulations; an immediate release formulation known in the art, and two different sustained release formulations of the present invention.

Figure 7 is a graph demonstrating the plasma concentration of guaifenesin over time in healthy human volunteers from an immediate release tablet lot which is known in the art, a non-layered modified release tablet lot of the present invention, and two bi-layered modified release tablet lots of the present invention (one comprising 600 mg of immediate release formulation and 600 mg of sustained release formulation and the other one comprising 400 mg of immediate release formulation and 800 mg of sustained release formulation).

Figure 8 is a graph demonstrating the dissolution profiles of four sustained release tablets of the present invention: one tablet is non-layered, comprising 1200 mg of sustained release formulation; another tablet is bi-layered, comprising 600 mg of sustained release formulation and 600 mg of immediate release formulation; another tablet is bi-layered, comprising 800 mg of sustained release formulation and 400 mg of immediate release formulation; and yet another tablet is bi-layered comprising 1000 mg of sustained release formulation and 200 mg of immediate release formulation.

Figure 9 is a graph demonstrating the plasma concentration of guaifenesin over an averaged 12 hour interval (taken from 11 twelve hour intervals over 5.5 days) in healthy human volunteers from an immediate release tablet lot known in the art and a bi-layered modified release tablet lot of the present invention.

Figure 10 is a graph demonstrating the plasma concentration of guaifenesin over time (the last twelve hour interval of the 11 twelve hour intervals described above) in

healthy human volunteers from an immediate release tablet lot known in the art and a bi-layered modified release tablet lot of the present invention.

Figure 11 is a graph demonstrating the averaged plasma concentration of guaifenesin over a 16 hour period in 27 healthy human volunteers from 600 mg bi-layered modified release tablets of the present invention administered to fasting volunteers, 1200 mg bi-layered modified release tablets of the present invention administered to fasting volunteers, and 1200 mg bi-layered modified release tablets of the present invention administered to volunteers who had been fed a high fat meal.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a novel modified release formulation comprising guaifenesin. In a preferred embodiment, a modified release formulation comprises a combination of a hydrophilic polymer in a ratio range of about one-to-one (1:1) to about six-to-one (6:1), more preferably a range of about three-to-two (3:2) to about four-to-one (4:1), and most preferably about two-to-one (2:1), with a water-insoluble polymer. The sustained release formulation may be compressed into a tablet. The present invention also relates to a novel compressed tablet which is made of two portions (a bi-layer tablet): a portion which comprises a modified release formulation of the present invention and a portion which is an immediate release formulation.

a) Sustained Release Formulation

In one embodiment of the present invention, a sustained release formulation comprises guaifenesin mixed with a polymer blend which consists of at least one hydrophilic polymer and at least one water-insoluble polymer. In a further embodiment, the sustained release formulation may comprise a combination of guaifenesin and at least one other drug including, but not limited to, an antitussive such as dextromethorphan hydrobromide, a decongestant such as phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine hydrochloride or ephedrine, an antihistamine such as chlorpheniramine maleate, brompheniramine maleate, phenindamine tartrate, pyrilamine maleate, doxylamine succinate, phenyltoloxamine citrate, diphenhydramine hydrochloride, promethazine, and clemastine fumerate, or a combination thereof.

Hydrophilic polymers suitable for use in the sustained release formulation include: one or more natural or partially or totally synthetic hydrophilic gums such as acacia, gum tragacanth, locust bean gum, guar gum, or karaya gum, modified cellulosic substances

such as methylcellulose, hydroxomethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethylcellulose, carboxymethylcellulose; proteinaceous substances such as agar, pectin, carrageen, and alginates; and other hydrophilic polymers such as carboxypolymethylene, gelatin, casein, zein, bentonite, magnesium aluminum silicate, polysaccharides, modified starch derivatives, and other hydrophilic polymers known to those of skill in the art or a combination of such polymers.

These hydrophilic polymers gel and dissolve slowly in aqueous acidic media thereby allowing the guaifenesin to diffuse from the gel in the stomach. When the gel reaches the intestines, it dissolves in controlled quantities in the higher pH medium, where the guaifenesin itself is fairly absorbable, to allow sustained release of guaifenesin throughout the digestive tract. Preferred hydrophilic polymers are the hydroxypropyl methylcelluloses such as those manufactured by The Dow Chemical Company and known as METHOCEL ethers. In one preferred embodiment of a sustained release formulation the hydrophilic polymer is a METHOCEL ether known as METHOCEL E10M.

Water-insoluble polymers which are suitable for use in the sustained release formulation are polymers which generally do not dissolve in solutions of a pH below 5, and dissolve more slowly in basic solutions than the hydrophilic polymer. Because the polymer is insoluble in low pH environments such as those found in gastric fluid, it aids in retarding drug release in those regions. Likewise, because the polymer dissolves more slowly in solutions of higher pH than hydrophilic polymers, it aids in retarding drug release throughout the intestines. This overall delayed release results in a more uniform serum concentration of guaifenesin.

The water-insoluble polymers suitable for use in this invention include: polyacrylic acids, acrylic resins, acrylic latex dispersions, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate and other polymers common to those of skill in the art. In a preferred embodiment, a sustained release formulation comprises the acrylic resin CARBOPOL 974P supplied by BF Goodrich.

A sustained release formulation of the present invention may further comprise pharmaceutical additives including, but not limited to: lubricants such as magnesium stearate, calcium stearate, zinc stearate, powdered stearic acid, hydrogenated vegetable oils, talc, polyethylene glycol, and mineral oil; colorants such as Emerald Green Lake and various FD&C colors; binders such as sucrose, lactose, gelatin, starch paste, acacia, tragacanth, povidone polyethylene glycol, Pullulan and corn syrup; glidants such as colloidal silicon

dioxide and talc; surface active agents such as sodium lauryl sulfate, dioctyl sodium sulfosuccinate, triethanolamine, polyoxyethylene sorbitan, poloxalkol, and quarternary ammonium salts; preservatives and stabilizers; excipients such as lactose, mannitol, glucose, fructose, xylose, galactose, sucrose, maltose, xylitol, sorbitol, chloride, sulfate and phosphate salts of potassium, sodium, and magnesium; and/or any other pharmaceutical additives known to those of skill in the art. In one preferred embodiment, a sustained release formulation further comprises magnesium stearate and Emerald Green Lake. In another preferred embodiment, a sustained release formulation further comprises magnesium stearate and FD&C Blue #1 Aluminum Lake Dye.

A sustained release formulation of the present invention may comprise at least one drug ingredient, at least one hydrophilic polymer, at least one water-insoluble polymer, and at least one pharmaceutical additive in any appropriate percent quantity which permits dissolution of drug ingredients that results in a therapeutically effective serum concentration profile for a full twelve hours. In a preferred embodiment, a sustained release formulation comprises approximately 95.5% guaifenesin, approximately 2.4% hydroxypropyl methylcellulose, approximately 1.2% acrylic resin, approximately 0.5% magnesium stearate, and approximately 0.3% colorant such as Emerald Green Lake or FD&C Blue #1.

The present inventive sustained release formulation controls release of guaifenesin into the digestive tract slowly over time. The drug guaifenesin experiences a shift in water solubility as the pH of the environment in which it resides (i.e. stomach versus intestinal tract) changes. In a more acidic environment, such as that found in the stomach, guaifenesin is less soluble while in a higher pH environment, such as that found in the intestines, guaifenesin is readily soluble. Dissolution rate of guaifenesin throughout the digestive tract is thus of primary importance in determining concentrations of guaifenesin attained in the blood and tissues as a drug formulation is digested.

To maintain a blood concentration of guaifenesin which provides good therapeutic effect, the release, or dissolution, of guaifenesin from a formulation matrix is preferably retarded and/or controlled through the intestines. The combination of hydrophilic and water-insoluble polymers of the sustained release formulation of the present invention gels when exposed to media of low pH. This creates a matrix out of which guaifenesin can diffuse. When the gelled polymer combination is exposed to media of a higher pH, the gel begins to slowly dissolve thereby releasing guaifenesin at a controlled rate.

In a preferred embodiment of the present invention, a sustained release formulation comprises a hydrophilic polymer, preferably hydroxypropyl methylcellulose, in a ratio range of about one-to-one (1:1) to about six-to-one (6:1), more preferably a range of about three-to-two (3:2) to about four-to-one (4:1), and most preferably about two-to-one (2:1), with a water-insoluble polymer, preferably acrylic resin. Further in a preferred embodiment, a sustained release formulation comprises not more than 6% hydrophilic polymer. In another preferred embodiment, a sustained release formulation comprises not more than 2.5% hydrophilic polymer. The inventors have discovered that this combination results in a serum concentration profile of guaifenesin that provides an optimal therapeutic concentration for at least twelve hours.

A sustained release formulation of the present invention may be manufactured according to any appropriate method known to those of skill in the art of pharmaceutical manufacture. In one embodiment, guaifenesin and a hydrophilic polymer may be mixed in a mixer with an aliquot of water to form a wet granulation. The granulation may be dried to obtain hydrophilic polymer encapsulated granules of guaifenesin. The resulting granulation may be milled, screened, then blended with various pharmaceutical additives, water insoluble polymer, and additional hydrophilic polymer. The formulation may then tableted and may further be film coated with a protective coating which rapidly dissolves or disperses in gastric juices.

A preferred embodiment of a method of preparing a sustained release formulation of the present invention may comprise loading approximately 126 kg of GUAIFENESIN and about 2 kg of METHOCEL E10M into a high shear mixer. The METHOCEL E10M and GUAIFENESIN may be mixed for about seven minutes at a mixing speed of about 150 RPM and a chopper speed of about 2000 RPM. The mixing and chopping speeds may then be increased to about 200 RPM and 3000 RPM respectively for about five minutes while about 49 kg of water are added to the mixer contents. The mixer may be run for two additional minutes to complete granulation. In a further preferred embodiment, the shut off for the mixer load is set to 21 kilowatts.

The wet granulation may be emptied into a fluid bed bowl and placed into a fluid bed dryer set to a dryer air flow of 900 CFM and an inlet temperature of about 50 to about 55°C until the outlet temperature increases at a rate of 1° per minute. The air flow may then be decreased to 600 CFM, and the inlet temperature may be decreased to 43°C until the granulation is dried to a moisture content of no more than 0.5%. In another preferred

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embodiment, the outlet temperature is set to a cut-off of 48°C. In yet another preferred embodiment, an agitator in the fluid bed bowl may be run intermittently during drying. The dried granulation may be passed through a mill fitted with a suitable screen size so that not more than about 30% of the resulting granulation comes through a 100 mesh screen and not more than about 10% of the resulting granulation is retained on a 10 mesh screen. In one preferred embodiment, the dried granulation may be passed through a mill fitted with a 0.109" size screen at a mill speed of about 500 to about 1500 RPM and a screw feed rate of about 35 to about 45 RPM. The resulting screened granulation is about 95% GUAIFENESIN and is called GUAIFENESIN DC (Direct Compressed) herein after. Screened granulation may be transferred to a 10 cubic foot V blender, combined with about another 0.6 kg of METHOCEL E10M, about 0.3 kg of a colorant such as EMERALD GREEN LAKE or FD&C BLUE #1, about 0.7 kg of magnesium stearate, and about 1.3 kg of CARBOPOL 974P. The combination may be blended for about three minutes.

The resulting formulation may further be compressed on a tablet compressor machine using tooling to form tablets. The tablets may be any appropriate weight, size, and shape depending on the desired dosage strength of tablet. In one embodiment, these tablets may further be loaded into a coating pan and film coated with OPADRY Y-S-3-714 (supplied by COLORCON, INC.) and air dried in the pan.

Another embodiment of a method of preparing a sustained release formulation of the present invention may comprise blending the drug ingredients, hydrophilic polymer, water insoluble polymer, and any pharmaceutical additives. The resulting blend may then be compressed into tablets and, if desired, film coated with a protective coating which rapidly dissolves or disperses in gastric juices. In a preferred embodiment of such a method, about 126 kg of GUAIFENESIN DC (about 95% purity), about 2.6 kg of METHOCEL E10M, about 1.3 kg of CARBOPOL 974P and about 0.333 kg of a colorant such as EMERALD GREEN LAKE or FD&C BLUE #1 may be loaded into a 10 cubic foot V BLENDER. The ingredients may be blended for about 20 minutes at which time about 0.6 kg of magnesium stearate may be added to the blended ingredients. This mixture may be blended for about another 10 minutes. The resulting formulation may further be compressed on a tablet compressor machine using tooling to form tablets. The tablets may be any appropriate weight, size, and shape depending on the desired dosage strength of the tablet. These tablets may further be loaded into a coating pan and film coated with OPADRY Y-S-3-714 (supplied by COLORCON, INC.) and air dried in the pan.

Tablets comprising a sustained release formulation of the present invention were prepared and tested for both *in vitro* and *in vivo* release characteristics as described in Examples 1, 2, and 3 below. In the *in vitro* testing, the dissolution rates of these tablets were compared against modified release tablets formulated without acrylic resin (EXAMPLE 1), and three commercially available tablets, one being an immediate release formulation and the other two being modified release formulations. Tablets comprising the sustained release formulation of the present invention demonstrated a slower, more controlled release of guaifenesin over a twelve hour period than any of the other tablets (see EXAMPLE 1 and 2, and Figures 4 and 5).

In the *in vivo* testing, serum concentrations of subjects taking tablets comprising the sustained release formulation of the present invention were compared with serum concentrations of subjects taking immediate release guaifenesin tablets and modified release guaifenesin tablets formulated without acrylic resin (see EXAMPLE 3 and Figure 6). Tablets comprising the sustained release formulation of the present invention demonstrated improved sustained release and therapeutic concentration at extended time periods that the other two formulations. However, in the subjects taking tablets comprising the sustained release formulation of the present invention, it took longer for guaifenesin to appear in the blood stream and the maximum serum concentration (Cmax) of guaifenesin in these subject was less than half of that of the subjects taking the immediate release tablets.

(b) <u>Bi-Layer Tablets</u>

To improve the Cmax and speed of appearance of guaifenesin in patients while maintaining therapeutic effect for at least twelve hours, a portion of a sustained release formulation of the present invention as described above may be combined with a portion of an immediate release formulation in a bi-layer tablet.

The immediate release formulation may comprise guaifenesin and various pharmaceutical additives such as lubricants, colorants, binders, glidants, surface active agents, preservatives, stabilizers, as described above and/or any other pharmaceutical additives known to those of skill in the art. In a preferred embodiment, an immediate release formulation comprises guaifenesin, microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. In a further preferred embodiment, an immediate release formulation may comprise about 58% guaifenesin, about 33% microcrystalline cellulose, about 8% sodium starch glycolate, and about 0.3% magnesium stearate.

The bi-layer tablet may be manufactured according to any method known to those of skill in the art. The resulting tablet may comprise the two portions compressed against one another so that the face of each portion is exposed as either the top or bottom of the tablet, or the resulting tablet may comprise the sustained release portion in the center coated by the immediate release portion so that only the immediate release portion is exposed. In a preferred embodiment, a bi-layer tablet of the present invention comprises the two portions compressed against one another so that the face of each portion is exposed.

In a preferred method of manufacturing the bi-layer tablets of the present invention a sustained release formulation is prepared according to either a wet granulation or dry granulation method as described above. The immediate release formulation may be prepared by simply blending the guaifenesin with any pharmaceutical additives. In a further preferred embodiment, appropriate quantities of GUAIFENESIN DC, microcrystalline cellulose, and sodium starch glycolate are blended in a 10 cubic foot blender for about twenty minutes. An appropriate quantity of magnesium stearate is then added to the ingredients and blended for about ten more minutes to make an immediate release formulation. Portions of the sustained release formulation and immediate release formulation are then compressed by a tablet compressor machine capable of forming bi-layer tablets. In one embodiment, these tablets may further be coated with a protective film which rapidly disintegrated or dissolves in gastric juices.

The tablets may be made with any ratio of sustained release to modified release formulation which results in a blood profile demonstrating appropriate therapeutic effect over extended time periods. In one preferred embodiment, the bi-layer tablets comprise portions of sustained release formulation and immediate release formulation which result in about a five-to-one (5:1) ratio of guaifenesin respectively. For example, in a 1200 mg bi-layer modified release guaifenesin tablet of the present invention, there may be about 200 mg of guaifenesin in the immediate release layer and about 1000 mg of guaifenesin in the sustained release layer.

In one preferred embodiment of manufacturing a 1200 mg bi-layer modified release guaifenesin tablet, about 105 kg of GUAIFENESIN DC, about 2.5 kg of METHOCEL E10M, about 1.25 kg of CARBOPOL 974P, and about 0.333 kg of EMERALD GREEN LAKE or FD&C BLUE #1 in a 10 cubic foot P.K. blender for about twenty minutes. About 0.6 kg of magnesium stearate may then be added and blending continued for about another ten minutes to prepare the sustained release formulation. Approximately 21 kg of

GUAIFENESIN DC, approximately 11.75 kg of microcrystalline cellulose, and approximately 3 kg of sodium starch glycolate may be blended in a 3 cubic foot P.K. blender for about twenty minutes. Approximately 0.1 kg of magnesium stearate may then be added and blending continued for about another ten minutes to prepare the immediate release formulation. The two formulations may then be compressed to make bi-layer tablets wherein about 75% of each tablet may be sustained release formulation and about 25% if each tablet may be immediate release formulation. The tablets may be any dosage strength, size, or shape. In a preferred embodiment, 1200 mg tablets are round and about 5/8 inch in diameter, about 0.28 inch - 0.31 inch in thickness, weigh about 1.46 grams and have a hardness range of about 15-40 SCU. In another preferred embodiment, 600 mg tablets are round and about 1/2 inch in diameter, about 0.218 inch – 0.230 inch in thickness, weigh about 0.729 grams and have a hardness range of about 12-30 SCU.

The immediate release portion of the bi-layer tablet is formulated to dissolve in aqueous media of low pH, such as that found in the stomach, to quickly release the guaifenesin contained within the portion. This results in rapid bioavailability of a high concentration of guaifenesin. As demonstrated in EXAMPLE 6 and Figures 9 and 10 below, the immediate release portion of the bi-layer tablet results in a maximum serum concentration (Cmax) and time of maximum serum concentration (Tmax) equivalent to that of immediate release tablets.

The sustained release portion gels when exposed to media of low pH allowing the sustained release portion of the tablet to be passed into the intestinal tract. In the intestines, the gelled sustained release portion is exposed to media of a higher pH, causing the gel to slowly dissolve, thereby allowing guaifenesin to diffuse and dissolve out of the gelled matrix. This results in controlled bioavailability over an extended time period (i.e. twelve or more hours) causing the tablet to provide extended therapeutic effect. This result is evidenced in EXAMPLE 6 and Figures 9 and 10 below – the half-life of the modified release bi-layer tablet is increased to more than 3 hours and the tablet has an AUCinf (the area under a plasma concentration versus time curve from time 0 to infinity) of greater than 8000 hr*μg/mL. As demonstrated in EXAMPLE 7 and Figure 11, the bi-layer tablets of the present invention had a further surprising result in that a 600 mg tablet had a Tmax equivalent to that of a 1200 mg and a Cmax and AUCinf approximately half of a 1200 mg tablet. Thus, without adjusting or changing the composition of the sustained release formulation or bi-layer tablet, a lower dosage strength guaifenesin tablet of the present invention exhibits plasma

concentration profile that is approximately directly proportional to that of a higher dosage strength guaifenesin tablet also of the present invention. As further demonstrated in EXAMPLE 7 and Figure 11, the bi-layer tablets of the present invention had another surprising result in that the Cmax and AUCinf of a 1200 mg tablet administered to volunteers who had been fasting and the Cmax and AUCinf of a 1200 mg tablet administered to volunteers who had consumed a high fat meal were approximately equivalent. Thus, a bi-layer tablet of the present invention demonstrates a reduced food effect, being approximately equally effective when administered to a patient on an empty or full stomach.

EXAMPLE 1

A batch of sustained release guaifenesin tablets, Lot# 7LB-31FC, with the following composition was prepared:

Components	Weight per Tablet
GUAIFENESIN DC	1260 mg
METHOCEL E10M	30 mg
EMERALD GREEN LAKE	4 mg
Magnesium Stearate	6.8 mg
Opadry Y-S-3-7413	13.01 mg

T0166

Another batch of sustained release guaifenesin tablets, Lot# 7LB-32FC, with the following composition was prepared :

Components	Weight per Tablet
GUAIFENESIN DC	1260 mg
METHOCEL E10M	30 mg
CARBOPOL 974P	15 mg
EMERALD GREEN LAKE	4 mg
Magnesium Stearate	6.8 mg
Opadry Y-S-3-7413	13.16 mg

T0161

Six tablets from Lot 7LB-31FC and six tablets from Lot 7LB-32FC were tested for *in vitro* guaifenesin release using an Acid/Base dissolution (slightly modified USP 23/NF 18 <711> Drug Release using Apparatus 2). Six dissolution vessels of a USP

calibrated Hanson dissolution bath, equipped with shafts and paddles, were filled with 675 ml of 0.1N hydrochorlic acid at 37.0°C. The bath and vessels were maintained at a temperature of 37.0 ± 0.5°C throughout the 12 hr. dissolution test. The paddles were set to rotate at 50 RPM and slowly lowered into the vessels. One tablet of lot 7LB-31 was then dropped into each vessel.

At the one hour and two hour intervals of testing, 5 mL samples of dissolution solution were withdrawn from each vessel and filtered through a 10 micron polyethylene filter into glass HPLC vials. Immediately after the two hour samples were withdrawn, 225 mL of 0.2M sodium phosphate tribasic was added to each vessel to increase the solution pH to about 6.8. The dissolution was run for ten more hours, 2.0 mL samples being withdrawn from each vessel at the 4 hr., 8 hr., 10 hr., and 12 hr. intervals. The filtered samples from each sampling interval were then run on an HPLC to determine percent guaifenesin released from each tablet at each of the sampling intervals.

The same dissolution testing procedure was performed for lot 7LB-32 FC. The lots gave dissolution profiles shown below and depicted in Figure 4.

Lot 7LB-31

T,0170

Vessel #	1 HR	2 HR	4 HR	8 HR	10 HR	12 HR
1	26	38	55	77	84	88
2	27	39	54	75	81	86
3	22	37	50	73	78	85
4	23	33	47	64	73	79
5	25	36	52	75	81	86
6	24	35	49	74	81	87
Average	**24.5**	**36.3**	**51.2**	**73.0**	**79.7**	**85.2**

Lot 7LB-32FC

T,0171

Vessel #	1 HR	2 HR	4 HR	8 HR	10 HR	12 HR
1	25	36	42	54	59	64.0
2	24	35	42	55	61	66
3	26	38	45	59	65	69
4	24	35	42	54	60	65

Vessel #	1 HR	2 HR	4 HR	8 HR	10 HR	12 HR
5	24	36	43	54	59	64
6	23	34	38	50	55	59
Average	**24.3**	**35.7**	**42.0**	**54.3**	**59.8**	**64.5**

Both formulations demonstrated sustained release of guaifenesin over a 12 hour period. Lot 7LB-32FC demonstrated identical release properties to Lot 7LB-31FC in 0.1N HCl. In buffered solution, however, Lot 7LB-32FC, the lot comprising a 2:1 ratio of METHOCEL E10M to CARBOPOL 974P, demonstrated a statistically slower release than Lot 7LB-31FC, comprising METHOCEL E10M and no CARBOPOL 974P. A slower release rate *in vitro* translates to a slower, more controlled release with longer drug action *in vivo* – a favorable characteristic for pharmaceutical products containing a high concentration of an active ingredient with a short half-life.

EXAMPLE 2

A dissolution study was run to compare dissolution profiles of lots 7LB-32FC and 7LB-31FC with currently available guaifenesin dosage forms. One immediate release tablet, ORGANIDIN NR, and two sustained release tablets, HUMIBID L.A. and DURATUSS, were subjected to the same dissolution study as described for lots 7LB031FC and 7LB-32FC in Example 1 above. The following is a summary of the results which are also depicted in Figure 5.

	ORGANIDIN NR % guaifenesin released	HUMIBID L.A. % guaifenesin released	DURATUSS % guaifenesin released
1 Hr	100	36	24
2 Hr	103	51	35
4 HR	104	72	47
8 HR	103	91	75
10 HR	103	96	86
12 HR	105	100	92

The immediate release ORGANIDIN released 100% of guaifenesin content within the first hour of dissolution. The two sustained release dosage forms which are

currently available both demonstrated a slower release of guaifenesin. However, both the HUMIBID LA and DURATUSS released guaifenesin more rapidly than either Lot 7LB-31FC or 7LB-32FC. Both HUMIBID LA and DURATUSS would, therefore, exhibit a faster rate of release and thus a shorter lived therapeutic effect *in vivo*.

EXAMPLE 3

The *in vivo* behavior of sustained release tablets of Lot 7LB-31FC and Lot 7LB-32 FC from Example 1 were compared to the *in vivo* behavior of an immediate release formulation (ORGANIDIN NR). The open-label study involved 9 healthy volunteers averaging 38 ± 11.01 years of age with a range of 23 years to 55 years of age. The subjects weighed 175.56 ± 24.22 lbs. with a range of 143 to 210 lbs. One subject was female and the remainder were male. Each subject received either one 1200 mg dose of one of the two above described sustained release tablets or 400 mg every four hours for 3 doses of the immediate release formulation.

Blood samples (7 mL with sodium heparin as anticoagulant) were taken prior to dosing and at specific intervals up to 12 hours after dosing. All blood samples were chilled and centrifuged within 30 minutes of being drawn. The plasma was separated, transferred to a polypropylene tube, frozen at –20°C or below and stored frozen until being shipped for guaifenesin analysis.

The plasma samples were analyzed by a fully validated HPLC method. The results are depicted in Figure 6. This resulting plasma concentration v. time data was subjected to pharmacokinetic analysis using non-compartmental analysis with Winnonlin 1.5. The results of the pharmacokinetic parameters analysis are below.

Subject	Formulation	T_{max} (hr.)	C_{max} (μg/mL)	AUC_{0-12} (hr*μg/mL)	$T_{1/2}$ (hrs.)	AUC_{inf} (hr*μg/mL)
1	7LB-31FC	2.00	827.02	4817.20	4.64	6339.25
2	7LB-31FC	1.50	834.65	4695.89	2.71	5291.71
3	7LB-31FC	1.50	802.44	4142.14	3.44	4728.33
4	7LB-32FC	0.75	625.48	3034.31	5.78	5134.35
5	7LB-32FC	1.00	1052.00	5872.46	5.99	8298.33
6	7LB-32FC	2.00	1372.00	7924.35	5.53	9557.78

T0190

Subject	Formulation	T_{max} (hr.)	C_{max} (μg/mL)	$AUC_{0\text{-}12}$ (hr*μg/mL)	$T_{1/2}$ (hrs.)	AUC_{inf} (hr*μg/mL)
7	ORGANIDIN NR	0.50	2140.00	6921.94	0.86	7009.68
8	ORGANIDIN NR	4.25	18.17.00	6598.26	0.73	6674.65
9	ORGANIDIN NR	0.50	2831.00	9389.76	0.81	9570.91
Mean	7LB-31FC	1.67	821.37	4551.74	3.59	5453.10
Mean	7LB-32FC	1.25	1016.49	5610.37	5.77	7663.49
Mean	ORGANIDIN NR	1.75	2262.67	7636.65	0.80	7751.74
Ratio (%)	7LB-31FC/IR	95.24	36.30	59.60	448.27	70.35
Ratio (%)	7LB-32FC/IR	71.43	44.92	73.47	718.92	98.86

Subjects given the 1200 mg formulation 7LB-32FC reached maximum plasma guaifenesin concentrations of 1016 μg/mL in 1.25 hours and had an AUCinf of 7663 hr*μg/mL. The subjects given formulation 7LB-31FC reached maximum plasma guaifenesin concentrations of 821 μg/mL in 1.67 hours and had an AUCinf of 5453 hr*μg/mL. The subjects given the immediate release formulation, ORGANIDIN NR, reached maximum plasma guaifenesin concentrations of 2263 μg/mL in 1.75 hours (2 subjects peaked at 0.5 hours after the first dose and the third peaked at 0.25 hours after the second dose at 4 hours) and had an AUCinf of 7752 hr*μg/mL. The two controlled release formulations demonstrated sustained release in that their half-lives were longer, 5.77 hours for the 7LB-32FC and 3.59 hours for the 7LB-31 FC compared to 0.8 hours for the immediate release formulation, ORGANIDIN NR.

Both formulations 7LB-32FC (with both METHOCEL E10M and CARBOPOL 974P) and 7LB-31FC (with METHOCEL E10M only) control the release of guaifenesin from the tablet compared to the immediate release ORGANIDIN NR. Formulation 7LB-32FC, the formulation containing a 6:1 ratio of METHOCEL E10M to CARBOPOL 974P, had the longest half life at 5.77 hours with the largest AUCinf between the two sustained release formulation. However, both sustained release formulation has a Cmax that was less than half of the Cmax of the immediate release ORGANIDIN NR.

EXAMPLE 4

Three different modified release tablet lots were prepared with the following compositions:

Modified Release Formulation I, non-layered tablet

T,0216

Components	Weight per Tablet
GUAIFENESIN DC	1260 mg
METHOCEL E10M	40 mg
CARBOPOL 974P	20 mg
Emerald Green Lake	4 mg
Magnesium Stearate	6.8 mg

Modified Release Formulation II, bi-layered, 400 mg IR and 800 mg MR

IR Formulation

T,0211

Components	Weight per Tablet
GUAIFENESIN DC	421 mg
Microcrystalline Cellulose (AVICEL)	40 mg
Sodium Starch Glycolate (EXPLOTAB)	60 mg
Magnesium Stearate	2 mg

SR Formulation

T,0212

Components	Weight per Tablet
GUAIFENESIN DC	842 mg
METHOCEL E10M	27 mg
CARBOPOL 974P	13.5 mg
Emerald Green Lake	3 mg
Magnesium Stearate	4.5 mg

Modified Release Formulation III, bi-layered, 600 mg IR and 600 mg SR

IR Formulation

T,0213

Components	Weight per Tablet
GUAIFENESIN DC	630.8 mg
Microcrystalline Cellulose (AVICEL)	353 mg
Sodium Starch Glycolate (EXPLOTAB)	90.1 mg
Magnesium Stearate	3 mg

SR Formulation

Components	Weight per Tablet
GUAIFENESIN DC	630.8 mg
METHOCEL E10M	40 mg
CARBOPOL 974P	20 mg
Emerald Green Lake	4 mg
Magnesium Stearate	6.8 mg

The *in vivo* behavior of each of the three modified release tablets and an immediate release formulation (ORGANIDIN NR) were compared. The open-label study involved 15 healthy volunteers averaging 31.67 ± 11.89 years of age with a range of 20 years to 51 years of age. The subjects weighed 162.00 ± 25.05 lbs. with a range of 123 to 212 lbs. All 15 subjects were administered 400 mg of the immediate release formulation every 4 hours for a total of 12 hours in on one day. On another day, 5 subjects were administered Modified Formulation I, another 5 subjects were administered Modified Formulation II, and yet another 5 subjects were administered Modified Formulation III.

Blood samples (7 mL with sodium heparin as anticoagulant) were taken prior to dosing and at specific intervals up to 12 hours after dosing. All blood samples were chilled and centrifuged within 30 minutes of being drawn. The plasma was separated, transferred to a polypropylene tube, frozen at –20°C or below and stored frozen until being shipped for guaifenesin analysis.

The plasma samples were analyzed by a fully validated HPLC method. The results are depicted in Figure 7. This resulting plasma concentration v. time data was subjected to pharmacokinetic analysis using non-compartmental analysis with Winnonlin 1.5. The results of the pharmacokinetic parameters analysis are below.

	Formulation	T_{max} (hr.)	C_{max} (μg/mL)	AUC_{0-12} (hr*μg/mL)	$T_{1/2}$ (hrs.)	AUC_{inf} (hr*μg/mL)
Mean	ORGANIDIN NR	0.90	2609.40	8768.40	1.28	9082.78
Mean	MR I	2.30	1631.40	5549.30	2.88	6044.93
Mean	MR II	2.30	2415.40	7304.38	1.48	7509.78
Mean	MR III	1.95	2938.00	8904.62	2.05	9161.03

T,0230

Modified Formulations II and III exhibited a Cmax more comparable to the immediate release formulation and an increased AUCinf from that of the non-layered Modified Formulation I. However, the half-lives of both Modified Formulation II and III were reduced from the half-life of Modified Formulation I. Although these bi-layer tablets showed an improved serum concentration of guaifenesin and an increased overall concentration with time, their half-life was compromised.

EXAMPLE 5

A dissolution study was run to compare dissolution profiles of Formulation I, Formulation II and Formulation III prepared as defined in EXAMPLE 4 above, and Formulation IV, a bi-layer tablet lot with 200 mg IR and 1000 mg SR prepared with the following composition:

IR Formulation

T,0231

Components	Weight per Tablet
GUAIFENESIN DC	211 mg
Microcrystalline Cellulose (AVICEL)	118 mg
Sodium Starch Glycolate (EXPLOTAB)	30 mg
Magnesium Stearate	1 mg

SR Formulation

Components	Weight per Tablet
GUAIFENESIN DC	1053 mg
METHOCEL E10M	25 mg
CARBOPOL 974P	12.5 mg
EMERALD GREEN LAKE	3.3 mg
Magnesium Stearate	5.7 mg

T,0240

The following is a summary of the results which are also depicted in Figure 8.

	Formulation I % released	Formulation II % released	Formulation III % released	Formulation IV % released
1 hr	22	45	38	29
2 hr	34	54	46	38
4 hr	43	65	56	48
6 hr	50	70	61	53
8 hr	58	73	66	60
10 hr	62	78	70	66
12 hr	66	81	75	71

T,0240

Formulation I, the non bi-layered tablet, demonstrated the slowest release of GUAIFENESIN. Formulation II and Formulation III had the fastest rates of release and would, therefore, exhibit a faster rate of release and thus a shorter lived therapeutic effect *in vivo*. Formulation IV has a rate of release which was faster than Formulation I, comprising no immediate release blend, but slower than Formulation II and Formulation III, both comprising more immediate release blend than Formulation IV.

EXAMPLE 6

The *in vivo* behavior of Formulation IV bi-layered tablets, prepared as described above in EXAMPLE 5, was compared to an immediate release formulation (ORGANIDIN NR). The open-label, multiple dose, randomized, 2-way crossover study

involved 26 healthy volunteers averaging 31.31 ± 9.81 years of age with a range of 19 years to 50 years of age. The subjects weighed 166.77 ±29.83 lbs. The subjects were placed into one of two treatment groups. Group 1 received Formulation IV tablet with 240 mL of water after an overnight fast every 12 hours for 5 days and a single dose on day 6. Group 2 received 400 mg of ORGANIDIN NR (2 x 200 mg tablets) with 240 mL of water every 4 hours for 5 days and one 400 mg dose every four hours for a total of 3 doses on day 6.

Blood samples (5 mL with sodium heparin as anticoagulant) were taken prior to dosing on days 1, 4, 5, and 6. On Day 1, additional blood samples (5 mL with sodium heparin as anticoagulant) were also obtained at 0.5, 0.75, 1, 1.5, 2, 3, 4, 4.5, 4.75, 5, 5.5, 6, 7, 8, 8.5, 8.75, 9, 9.5, 10. 11, and 12 hours after the initial dose. On Day 6, additional blood samples (5 mL with sodium heparin as anticoagulant) were also obtained at 0.5, 0.75, 1, 1.5, 2, 3, 4, 4.5, 4.75, 5, 5.5, 6, 7, 8, 8.5, 8.75, 9, 9.5, 10, 11, 12, 14, 16, and 24 hours after the initial dose. Plasma was separated and the plasma frozen until analyzed for guaifenesin content. The resulting plasma concentration data was subjected to pharmacokinetic and statistical analysis in order to determine if the sustained release tablets performed as controlled release tablets at steady state.

The results of the pharmacokinetic parameters analysis are below.

Averaged Testing – 11 Twelve-Hour Intervals

T,025

	Formulation	T_{max} (hr.)	C_{max} (μg/mL)	AUC_{0-12} (hr*μg/mL)	$T_{1/2}$ (hrs.)	AUC_{inf} (hr*μg/mL)
Mean	ORGANIDIN NR	1.69	2463.20	8381.93	0.78	8528.51
Mean	Bi-layered Tablet	1.05	2111.38	7875.68	3.31	8686.08

The results of the testing are depicted in Figure 9.

Steady State Testing

T,025\

	Formulation	T_{max} (hr.)	C_{max} (μg/mL)	AUC_{0-12} (hr*μg/mL)	$T_{1/2}$ (hrs.)	AUC_{inf} (hr*μg/mL)
Mean	ORGANIDIN NR	2.03	2278.20	7751.23	0.88	7962.14
Mean	Bi-layered Tablet	0.86	2349.6	8202.47	3.61	9259.24

The results of the testing are depicted in Figure 10.

The 200/1000 mg bi-layered tablet exhibited a Cmax and a AUCinf equivalent to that of the immediate release blend, a short Tmax and an extended half-life. Thus, a bi-

layered tablet with 200 mg guaifenesin in the immediate release formulation and 1000 mg of guaifenesin in the sustained release formulation results in a tablet which delivers a high serum concentration in a short period of time, yet maintains an effective concentration of guaifenesin in the blood stream for a full twelve hours.

EXAMPLE 7

A study was performed to examine the relative bioavailability of two different dosage strengths of modified release guaifenesin formulations of the present invention as well as the effect of food on the relative bioavailability of a guaifenesin formulation of the present invention in normal, healthy male and/or female volunteers. Two batches of guaifenesin bi-layer tablets, one 600 mg and one 1200 mg, were prepared according to the following composition.

600 mg Tablet

IR Formulation

T,0260

Components	Weight per 200,000 Tablets
GUAIFENESIN DC	21.05 kg
Microcrystalline Cellulose (AVICEL PH102)	11.75 kg
Sodium Starch Glycolate (EXPLOTAB)	3.00 kg
Magnesium Stearate	0.10 kg

SR Formulation

T,0261

Components	Weight per 200,000 Tablets
GUAIFENESIN DC	105.27 kg
Hydroxypropyl Methyl Cellulose (METHOCEL E10M)	2.50 kg
Carbomer (CARBOPOL 974P)	1.25 kg
FD&C Blue #1 Aluminum Lake Dye	0.33 kg

Components	Weight per 200,000 Tablets
Magnesium Stearate	0.57 kg

1200 mg Tablet

IR Formulation

T/0270

Components	Weight per 100,000 Tablets
GUAIFENESIN DC	21.05 kg
Microcrystalline Cellulose (AVICEL PH102)	11.75 kg
Sodium Starch Glycolate (EXPLOTAB)	3.00 kg
Magnesium Stearate	0.10 kg

SR Formulation

T/0271

Components	Weight per 100,000 Tablets
GUAIFENESIN DC	105.27 kg
Hydroxypropyl Methyl Cellulose (METHOCEL E10M)	2.50 kg
Carbomer (CARBOPOL 974P)	1.25 kg
FD&C Blue #1 Aluminum Lake Dye	0.33 kg
Magnesium Stearate	0.57 kg

Note: the 600 mg and 1200 mg tablets were similarly prepared, the only difference between the dosage forms being that the 1200 mg tablet contained about twice as much of each ingredient as the 600 mg tablet.

The *in vivo* behaviors of a 600 mg tablet administered to volunteers in the fasting state (about 10 hours pre-dose until about 4 hours after dosing), the 1200 mg tablet administered to volunteers in the fasting state (about 10 hours pre-dose until about 4 hours after dosing), and the 1200 mg tablet administered to volunteers after a high fat meal

(consumed within 30 minutes of dosing) were compared. The open-label study involved 27 healthy volunteers between the ages of 18 and 55. The subjects weighed within 15% of their Ideal Body Weight as defined by the 1983 Metropolitan Life chart. The 27 volunteers were divided into 3 treatment groups, 9 receiving the 600 mg tablet, 9 receiving the 1200 mg tablet while fasting, and 9 receiving a 1200 mg tablet after consuming a high fat meal for Period 1 of the trial. After completion of Period 1, the volunteers were crossed-over for Period 2 (e.g. so that the 9 volunteers who had been receiving the 600 mg tablet in Period 1 received the 1200 mg tablet while fasting in Period 2). After completion of Period 2, the volunteers were crossed-over again into their 3rd and final treatment group (i.e. the 9 volunteers who received the 1200 mg tablet while fasting in Period 2 and the 600 mg tablet while fasting in Period 1 received the 1200 mg tablet after consumption of a high fat meal in Period 3). Each volunteer was administered one dose of the appropriate tablet and then monitored over a 16 hour period.

Blood samples (7 mL with sodium heparin as anticoagulant) were taken about one hour prior to dosing and at specific intervals up to 16 hours after dosing (at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, and 16 hours). All blood samples were chilled and centrifuged within 30 minutes of being drawn. The plasma was separated, transferred to a polypropylene tube, frozen at –20°C or below and stored frozen until being shipped for guaifenesin analysis. The volunteers were then given at least a seven day washout period (where no guaifenesin was administered to them under the study) prior to being crossed-over to the next treatment group.

The plasma samples were analyzed by a fully validated HPLC method. The results are depicted in Figure 11. This resulting plasma concentration v. time data was subjected to pharmacokinetic analysis using non-compartmental analysis with Winnonlin 1.5. The results of the pharmacokinetic parameters analysis are below.

	Formulation	T_{max} (hr.)	C_{max} (μg/mL)	AUC_{0-12} (hr*μg/mL)	$T_{1/2}$ (hrs.)	AUC_{inf} (hr*μg/mL)
Mean	600 mg Fasted	0.81	1074.26	3623.03	2.33	3676.23
Mean	1200 mg Fasted	0.94	1948.62	7483.20	3.33	7912.61
Mean	1200 mg Fed	2.18	1988.08	7424.20	0.91	7425.29

T0280

The 600 mg tablet demonstrated a serum profile approximately directly proportional to the serum profile of the 1200 mg tablet. The Cmax of the 600 mg tablet was

about 55% that of the 1200 mg tablet. The AUC_{0-12} of the 600 mg tablet was about 48% that of the 1200 mg tablet and the AUCinf of the 600 mg tablet was about 46% that of the 1200 mg. improved serum concentration of guaifenesin and an increased overall concentration with time, their half-life was compromised.

The 1200 mg tablet demonstrated that the bi-layer tablets of this invention greatly reduce the food effect in bioavailability and serum concentration of guaifenesin. The Cmax of the 1200 mg tablet administered after a high fat meal (fed tablet) was about 102% of the Cmax of the 1200 mg tablet administered after fasting (fasted tablet). The AUC_{0-12} of the 1200 mg fed tablet was about 99% that of the fasted tablet and the AUCing of the 1200 mg fed tablet was about 94% that of the fasted tablet.

Other embodiments and uses of the invention will be apparent to those of skill in the art from consideration of the specification and practice of the invention disclosed herein. The specification and examples should be considered exemplary only with the true scope and spirit of the invention indicated by the following claims. As will be easily understood by those of skill in the art, variations and modifications of each of the disclosed embodiments can be easily made within the scope of this invention as defined by the following claims.